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Nicotine caused apoptosis in human renal proximal tubular epithelial cells via NF-κB signaling pathway and G2/M phase cell cycle arrest

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Background: Nicotine is, to a large extent, responsible for smoking-mediated renal dysfunction. This study investigated nicotine's effects on renal tubular epithelial cell apoptosis *in vitro* and it explored the mechanisms underlying its effects.
Methods: Human proximal tubular epithelial (HK-2) cells were treated with nicotine. Intracellular levels of reactive oxygen species (ROS) and the expression of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) proteins were determined. The messenger ribonucleic acid and protein expression associated with the nicotine acetylcholine receptors (nAChRs) in HK-2 cells was examined, and apoptosis was detected using cell cycle analysis, and immunoblot analysis.
Results: The HK-2 cells were endowed with nAChRs. Nicotine treatment reduced cell viability dose dependently, increased ROS levels, and increased extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK expression. Nicotine increased NF-κB activation, which was attenuated by N-acetyl-L-cysteine, and ERK and JNK inhibitors, but was not affected by a p38 MAPK inhibitor. Nicotine increased the Bax/Bcl-2 ratio, which was attenuated by N-acetyl-L-cysteine, the NF-κB inhibitor, Bay 11-7082, and hexamethonium, a non-specific nAChR blocker. Flow cytometry revealed nicotine-induced G2/M phase arrest. While nicotine treatment increased the expression of phosphorylated cdc2 and histone H3, a marker of G2/M phase arrest, hexamethonium and Bay 11-7082 pretreatment reduced their expression.
Conclusion: Nicotine caused apoptosis in HK-2 cells by inducing ROS generation that activated the NF-κB signaling pathway via the MAPK pathway and the arrest of the cell cycle at the G2/M phase. Nicotine-induced apoptosis in HK-2 cells involves the nAChRs.

Keywords: apoptosis, nicotine, reactive oxygen species, signal transduction